THE PREVALENCE AND THE ASSOCIATE FACTORS FOR THYROID MALIGNANCY IN LARGE GOITERS

Results from Six Years' Experience in Hospital Raja Perempuan Zainab II

By

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LIST OF ABBREVIATIONS AND NOMENCLATURES

AACE	American Association of Clinical Endocrinologists
AME	Associazione Medici Endocrinologi
B	Coefficient Regression
CI	Confident Interval
CT	Computed Tomography
ETA	European Thyroid Association
FNAC	Fine needle aspiration cytology
HRPZ II	Hospital Raja Perempuan Zainab II
HPE	Histopathological Examination
IqR	Interquartile
MNG	Multinodular goiter
OR	Odds ratio
RLN	Recurrent Laryngeal Nerve
SD	Standard Deviation
SSI	Surgical site infection
STN	Solitary thyroid nodule
T3	Tri-iodothyronine
T4	Thyroxine
TSH	Thyroid Stimulating Hormone
US	Ultrasonography
WHO	World Health Organization

ABSTRACT IN MALAY

Latarbelakang:

Goiter besar merupakan satu masalah yang lazim ditemui dan dirawati oleh pakar bedah endokrin di negara membangun tetapi isu mengenai goiter besar jarang dibincangkan, terutamanya isu mengenai kaitan di antara goiter besar dan kanser tiroid. Objektif kajian ini ialah untuk menganalisa faktor-faktor yang berkaitan untuk kanser tiroid dalam goiter besar dan juga komplikasi pembedahan ke atas goiter besar.

Kaedah:

Rekod pesakit yang menjalani pembedahan primari tiroid dari Jun 2007 sehingga Mei 2013 dikaji. Pesakit akan dijadikan subjek kajian jika berat spesimen kelenjar tiroid daripada pembedahan 'hemithyroidectomy' ≥50g atau pembedahan 'total thyroidectomy' ≥100g. Factor yang berkaitan dengan kanser tiroid dalam goiter besar (umur, jantina, status fungsi tiroid, tanda-tanda tekanan oleh goiter dan 'nodularity') dikaji. Komplikasi pembedahan tiroid seperti 'hypoparathyroidism' sementara dan kekal, kecederaan 'RLN', pendarahan, infeksi pada luka kawasan bedah, kecederaan organ sekeliling dan kematian akan direkodkan.

Keputusan kajian:

Sebanyak 611 pesakit yang menjalani pembedahan tiroid dijadikan subjek dalam kajian ini. Kelaziman tiroid besar adalah 410 (67.1%) dan kelaziman kanser tiroid diantara goiter besar adalah 115 (28.0%). Pesakit dengan goiter besar mempunyai peluang yang lebih tinggi untuk menghidapi kanser tiroid dengan nisbah ganjil 1.52 (1.02, 2.28). Analisa

Logistik Regrasi Pelbagai menunjukkan bahawa peningkatan umur dan ‘solitary thyroid nodule (STN)’ merupakan factor-faktor yang mempunyai peluang yang lebih tinggi untuk menghidapi kanser tiroid dalam goiter besar, masing-masing dengan nisbah ganjil 1.02 (1.01, 1.04) dan 1.80 (1.10, 2.94). Seramai 82 (25.5%) mengalami ‘hypoparathyroidism’ sementara, 9 (2.8%) ‘hypoparathyroidism’ kekal, 4 (1.2%) kecederaan ‘recurrent laryngeal nerve (RLN)’, 8 (2.5%) pendarahan, 6 (1.8%) infeksi pada luka kawasan bedah, 4 (1.2%) kecederaan organ sekeliling dan 1 (0.3%) kematian.

Kesimpulan:

Kelaziman goiter besar yang tinggi di negara membangun memerlukan cara rawatan penyakit tiroid yang berbeza. Goiter besar adalah lebih lazim berkaitan dengan kanser tiroid. Disebabkan oleh keraguan mengenai sensitiviti ‘fine needle aspiration cytology (FNAC)’ untuk mengesahkan kanser tiroid dalam goiter besar, kita sepatutnya mempertimbangkan pembedahan lebih awal, terutamanya pesakit tua dan ‘STN’. Bagaimanapun, risiko pembedahan untuk goiter besar sepatutnya dipertimbangkan dan pembedahan ini sepatutnya hanya dilakukan oleh pakar dalam bidang ini.

ABSTRACT IN ENGLISH

Background:

Large goiters are very common and it is frequently encountered by endocrine surgeons especially in developing countries. Rarely, issues regarding large goiters have been discussed, particularly the association between large goiter and thyroid cancers. The objectives of this study are to analyze the associate factors of thyroid malignancy in large goiters as well as the surgical complications in performing resection for large goiters.

Methods:

Patients who had primary thyroid surgery between June 2007 and May 2013 were retrospectively reviewed. Patients who underwent thyroidectomy with a resected specimen of ≥ 50g in hemithyroidectomy or ≥ 100g in total thyroidectomy were recruited in the study. The associate factors for thyroid cancer in large goiters (age, gender, thyroid function status, compression symptom and, nodularity) were analyzed. The surgical complications namely temporary hypocalcaemia, permanent hypoparathyroidism, RLN injury, post-operative haemorrhage, surgical site infection, local structures injury and mortality associated with thyroid surgery were recorded.

Results:

A total of 611 patients who had capsular dissection thyroid surgeries were recruited in the study. The prevalence of large goiter was 410 (67.1%) and the prevalence of thyroid malignancy in large goiters was 115 (28.0%). The patients with large goiters had higher

chance to have thyroid malignancies with OR of 1.52 (1.02, 2.28). Multiple Logistic Regression Analysis revealed that the significant associate factors for thyroid malignancy in large goiters were age and STN with OR of 1.02 (1.01, 1.04) and 1.80 (1.10, 2.94), respectively. There were 82 (25.5%) temporary hypocalcaemia, 9 (2.8%) permanent hypoparathyroidism, 4 (1.2%) RLN injuries, 8 (2.5%) post-operative haemorrhages, 4 (1.2%) local structure injuries and 1 (0.3%) death after thyroid surgery for large goiters.

Conclusions:

The high prevalence of large goiters in the developing countries necessitates the different approach in the management of thyroid disease. Large goiters are associated with higher prevalence for thyroid malignancy. With the doubt of sensitivity in detecting thyroid malignancy from FNAC in large goiter, surgeons should consider removing the goiter early especially in older patients and those with STN. Nevertheless, the risks of surgery for large goiter should be deliberated and the surgery should only be performed by expert personal.

CHAPTER 1: INTRODUCTION

A goiter is defined as an enlargement of the thyroid gland. It is derived from the French *(goiter)* and Latin *(guttur)*, which both mean throat. It is a very common clinical problem. At least 4% of population in iodine-sufficient countries has palpable goiters and about 50% can be detected by using ultrasonography (Polyzos *et al.*, 2007). The disease often progress in time with the increase in size of the thyroid gland. However, the natural history of thyroid growth varies from patient to patient. It is very difficult to predict and monitor the growth of the thyroid gland. Furthermore, there is always a concern of the possibility that the goiter may harbour occult malignancy (Costamagna *et al.*, 2013; Miccoli *et al.*, 2006).

Goiters can be classified into toxic or non-toxic, endemic or non-endemic, diffuse or nodular. Nodular goiters are further classified into solitary thyroid nodule (STN) and multinodular goiter (MNG). Goiter is considered endemic when it involves more than 10% of the population. Iodine deficiency is the cause of endemic goiter especially in the developing countries. Sporadic or non-endemic goiters have the prevalence of 4-7% which the cause remains unclear and it is most probably multifactorial involving genetic and environmental factors (Daniels, 1996).

Thyroid malignancy is relatively rare compared to epithelial malignancy and it represents 1% of all human neoplasm (Curado, 2008). Although rare, thyroid malignancy remains the most frequent form of malignancy of endocrine glands. The incidence of thyroid cancer has increased for the past few decades in several developed countries (Burgess, 2002; Colonna *et al.*, 2002; Davies and Welch, 2014; Hodgson *et al.*, 2004). Many experts believe that the increased incidence of thyroid cancer is resulted primarily

from the availability of the more sensitive diagnostic procedures which increase the detection of small cancers in the preclinical stage. This is evidenced by the rise of the numbers of incidentalomas. Some suggested that the increased incidence is most likely due to a combination of an apparent increase due to higher detection rates and of a true increase, a possible consequence of increased population exposure to radiation and to other unrecognized carcinogens (Pellegriti *et al.*, 2013).

Many studies have been conducted to identify the risk factors for thyroid malignancy but the results obtained vary. In a study by Rios er al. reported that family history of thyroid pathology, personal history of cervical radiation therapy, prior surgery, and presence of cervical lymphadenopathies on physical exploration were the risk factors of thyroid malignancy (Rios *et al.*, 2004). Other associated risks for thyroid cancer include male gender, younger age, fewer nodules and smaller nodule size have also been reported (Luo *et al.*, 2012). A population-based study in Korea found that older age, female, overweight, higher monthly household income, higher educational level, and alcohol consumption were significant risk factors for thyroid cancer (Choi *et al.*, 2013).

Previously it was thought that MNG carries lower risk of malignancy as compared to STN. But recent studies showed the trend towards similar risk for malignancy and the incidence of malignancy in MNG should not be underestimated (Gandolfi *et al.*, 2004; Pradhan *et al.*, 2011; Sachmechi *et al.*, 2000). Traditionally, hyperthyroidism was once viewed as a protective factor for thyroid malignancy. In the year 1954, Sokal *et al*. showed that patients with hyperthyroidism had a higher incidence of thyroid carcinoma (Sokal, 1954). Since then, association between hyperthyroidism and thyroid malignancy had drawn a particular attention over the decades. Recent studies showed that a higher risk of

malignancy in patients with hyperthyroidism as compared to euthyroidism (Karagulle *et al.*, 2009; Negro *et al.*, 2013; Smith *et al.*, 2013).

There are only a few studies regarding large goiters. This is most probably due to lack of study subjects in non-endemic, developed countries (Heck *et al.*, 2007; Phitayakorn *et al.*, 2006). So far, there is no study regarding the prevalence and risk of malignancy in large goiters. Hence, lack of evidence-based study to suggest an optimal diagnostic tool and the role of surgery may potentially lead to mis-management of patients with large goiter. Large goiter is not an indication for surgery unless patient presented with pressure symptom, malignant disease or cosmetic issues (Gharib *et al.*, 2010). If large goiter is associated with thyroid cancer, this will alters our management in term of early surgical intervention, biopsy before the surgery and lastly, to subject patients for medical or radioiodine therapy which will delay the management of underlying malignant disease.

Ultrasonography (US) and fine needle aspiration cytology (FNAC) are routine pre-operative investigations for nodular goiter. Studies of US to detect malignancy in goiter show 20% rates of false negative and it is suggested that US was not reliably to exclude malignancy in a large thyroid nodule (Wharry *et al.*, 2013). Furthermore, FNAC in diagnosing thyroid malignancy has significant false negative rate ranged 5-50% especially in large goiter and in MNG (Akgul *et al.*, 2011; McCoy *et al.*, 2007; Pinchot *et al.*, 2009). If pre-operative investigations are not reliable to detect malignancy in large goiter, thyroidectomy is the only option to ensure the accurate diagnosis. The selection of patient with large goiter for early surgical intervention will be much dependent on other associate risks for malignancy. The issues of whether all patients with large goiters need surgery and the extent of thyroidectomy in large goiter remain to be answered.

Studies for complications after thyroidectomy for large goiter are scarce (Agarwal *et al.*, 2012; Gardiner and Russell, 1995). Both studies gave different rates of surgical complications in large goiters. Complications following thyroidectomy for large goiters are predicted to be more than thyroidectomy performed on small goiters. Safety is an issue to be considered when performing a thyroid surgery in large goiters. It shall be safe with minimum morbidity and mortality rate.

In Malaysia, we have more number of patients with large goiters due to long standing disease before seeking medical attention. Management plans in term of indication for surgery, type of surgery and the need for biopsy and US before the surgery might be different from what is being practiced in other part of the world. To determine the optimal clinical management of large goiter, we retrospectively reviewed the records of all patients who underwent thyroidectomy in the years 2007 through 2013. Our goals were, first, to calculate the prevalence of large goiter in thyroidectomy patients; second, to evaluate the prevalence of malignancy in large goiter; and, third, to determine the likelihood associate factors of thyroid malignancy in large goiters. We would also like to know the rate of complication and surgical outcome following thyroidectomy in large goiters. Perhaps, this will guide us in our management for patients with large goiters in the future.

CHAPTER 2: OBJECTIVES

To study the prevalence and the possible associated factors for thyroid malignancy in patients with large goiters.

Specific objectives

1. To determine the prevalence of large goiters among thyroidectomy patients.
2. To determine the prevalence of thyroid malignancy in patients with large goiters.
3. To determine the association between size of goiters and thyroid malignancy.
4. To identify the associated factors (demographic and clinical) of thyroid malignancy in large goiters.
5. To describe the proportion of the surgical outcome and complication rate following thyroidectomy for large goiters

Research Questions

1. How prevalent is large goiter observed among thyroidectomy patients?

2. How prevalent is thyroid malignancy observed in patients with large goiters?

3. Is there any significant association between size of goiters and thyroid malignancy?

4. Is there any significant association between demographic (age, gender) or clinical characteristics (nodularity, thyroid function status, pressure symptoms) and thyroid malignancy in large goiters?

5. What is the rate of complication (temporary hypocalcaemia, permanent hypoparathyroidism, recurrent laryngeal nerve (RLN) injury, haemorrhage, surgical site infection (SSI), other organs injury and mortality) following thyroidectomy for large goiters?

Research Hypothesis

Hypothesis 1

H_0: Large goiter is not associated with thyroid malignancy.

H_A: Large goiter is associated with thyroid malignancy.

Hypothesis 2

H_0: Age, gender, nodularity, thyroid function status and pressure symptoms are not associated with the risk of thyroid malignancy in large goiters.

H_A: Age, gender, nodularity, thyroid function status and pressure symptoms are associated with the risk of thyroid malignancy in large goiters.

CHAPTER 3: LITERATURES REVIEW

3.1 Large goiter

The weight of a normal thyroid gland is approximately 10 to 20 grams (Langer, 1999). A large goiter is defined as a resected specimen of more than or equal to 50g in hemithyroidectomy and more than or equal to 100g in total thyroidectomy. This defines a large goiter is at least five times greater than a normal thyroid gland. Review of the literatures unable to find the first author who describes the definition of large goiter. The earliest definition was made by Hamburger in 1985. The author defined large toxic MNGs as those having estimated weights of 100 g or more and massive goiters as those having weights 200g or more. The effect of radioiodine therapy in toxic MNG was studied by the author and the weight of the thyroid glands were estimated based on clinical palpation, thyroid imaging, or combinations of methods (Hamburger and Hamburger, 1985).

It is impossible to determine the exact weight of a thyroid gland before surgery. A literature review by Langer in 1999 stated that there are 3 ways to estimate the size of a thyroid gland: by post mortem thyroid weight, by palpation and, by ultrasound volumetry (Langer, 1999). Most of the endocrine surgeons prefer to estimate thyroid weight by palpation and this is entirely based on the experience with interpersonal bias. Ultrasound of thyroid had become famous for the past two to three decades. Estimation of thyroid glands volume can be done by using ultrasound. But the correlation between the volume and the weight is yet to be determined.

Phitayakarn *et al*. conducted a study regarding large goiter in United States. In this study, potential epidemiological variables associated with the development of large

nodular goiter were investigated. In the study, the definition of unilateral large goiter was ≥ 50g and bilateral large goiter was ≥ 100g. Our study used the same criteria to define unilateral and bilateral large goiters. According to the study, the incidence of large goiter among thyroidectomies patients was 23%. The factors associated with large goiter are African-American race (adjusted odds ratio 3.3, 95% CI = 2.0-5.4), obesity (adjusted odds ratio 2.5, 95% CI = 1.5-4.0) and age more than 40 years old (adjusted odds ratio 2.1, 95% CI = 1.2-3.8). Gender, family history, smoking and alcohol intake are not associated with higher risk of large goiter (Phitayakorn *et al.*, 2006).

3.2 Thyroid Malignancy

3.2.1 The incidence of thyroid cancer

Thyroid cancer is uncommon and represents only 1% of all malignancies. In year 2002, a report of thyroid cancer incidence in Australia was published based on the data from Australia's regional cancer registries. There were 9,053 new cases of thyroid cancer in Australia for the period 1982-1997. Papillary, follicular, medullary, anaplastic, and "other diagnoses," accounted for 65.8%, 17.8%, 4.6%, 1.3%, and 10.5% of registered cases respectively (Burgess, 2002). In France, data collected between the periods of 1978-1997 reported a total of 3853 adult cases of thyroid cancer. The incidence of thyroid cancer increased by 6.2% per year in men and by 8.1% per year in women (Colonna *et al.*, 2002). Similar report of increasing incidence of thyroid cancer was shown in an analysis by Hodgson *et al*. in Florida, United States between 1990 and 2000. The age-adjusted incidence rates increased from 4.2 per 100,000 to 7 per 100,000 in 2000 with estimated annual percent change of 5.5% ($P< 0.001$) in this period (Hodgson *et al.*, 2004).

Incidence of incidental cancer in patients operated for benign thyroid disease was in the increasing trend as reported by a study conducted by Costamagna *et al*. The study included a total of 568 patients underwent surgery for benign thyroid disease. Incidental cancer was found in 53 patients (9.3%) in which 44 (83.0%) had papillary, 4 (7.5%) follicular carcinoma, 4 (7.5%) medullary carcinoma and 1 (1.9%) had primitive thyroid paraganglioma (Costamagna *et al.*, 2013). The study carried out by Miccoli *et al*. revealed that a 10.4% of patients operated for benign thyroid disease had incidental thyroid malignancy from the final histopathology report (Miccoli *et al.*, 2006).

3.2.2 The association between thyroid cancer and large goiter

There was no study to evaluate the association between thyroid cancer and large goiter (defined by weight). The study conducted in 2007 by McCoy to evaluate the accuracy of FNAC to diagnose malignancy in thyroid nodules ≥ 4cm revealed that 26% of these patients had thyroid malignancy from final pathology after surgery. The false negative rate of FNAC is high and thyroid nodules ≥ 4 cm should be considered for diagnostic lobectomy regardless of FNAC results (McCoy *et al.*, 2007). Similar study was conducted in year 2009 which reported 13.5% of thyroid malignancy in patients with nodules ≥ 4cm. The false negative rate for FNAC was as high as 50% observed in this study (Pinchot *et al.*, 2009).

3.2.3 Risk factors for thyroid malignancy

Few studies had reported the different risk factors for thyroid malignancy. Most of the studies were conducted on MNG. Luo et al. conducted a study of 838 patients with MNG who underwent thyroidectomies and found that 31% of patients have thyroid malignancy from the final pathologic diagnosis. In this study, Luo et al. suggested that risk factors for malignancy in a MNG were male gender, younger age, fewer nodules, and smaller nodule size. Thyroid weight was not associated with the risk of malignancy (Luo *et al.*, 2012). In year 2005, Rios et al. described in his study that the risk factors for thyroid cancer in MNG are family history of thyroid pathology, personal history of cervical radiation therapy, prior surgery, and presence of cervical adenopathies (Rios *et al.*, 2004).

Based on the Korean National Health and Nutrition Examination Survey 2010-2011, the association between the socioeconomic status and thyroid cancer were reviewed.

The study was population-based and it was for all type of thyroid malignancies regardless of the types of goiter. Multivariable analysis revealed that older age (OR 1.03; 95%CI 1.00,1.05), female (OR 8.16; 95%CI 2.99,22.24), overweight (OR 1.04; 95%CI 1.01,1.06), higher monthly household income (OR 3.27; 95%CI 1.16,9.20) for medium-highest household income vs lowest household income; OR 3.30; 95%CI 1.16,9.34 for highest household income vs lowest household income), higher educational level (OR 2.74; 95%CI 1.16,6.46 for 10-12 years vs < 7 years) and alcohol consumption (OR 1.89; 95%CI 1.08,3.32) were significant risk factors for thyroid cancer (Choi *et al.*, 2013).

3.2.4 Thyroid malignancy in STN versus MNG

The difference in the prevalence of thyroid cancer in thyroid glands with STN versus MNG remains uncertain. Most of the studies showed more prevalence of thyroid cancer in STN than MNG. A meta-analysis was performed to evaluate the comparative prevalence of thyroid cancer in STN and MNG. Fourteen studies were recruited in the study. It encompassed 23565 patients with MNG and 20723 patients with STN. MNGs were found to have a lower risk of thyroid cancer than STN with OR 0.8 (0.67,0.96) (Brito *et al.*, 2013).

Study comparing malignancy in a nonfunctioning STN and MNG reported that malignant involvement in cold nodules of MNG did not differ significantly from that found in STN. In this study, thyroid scans were performed for all the subjects. FNAC was performed for all cold nodules in 146 patients and thyroid cancers were confirmed by final pathology report after surgery. The rate of malignancy in cold nodules in the MNG group was 9.78%, in comparison with 8% in the group with STN (P = 0.89). It was concluded

that no significant difference in the prevalence of malignancy in cold nodules in MNG and STN (Sachmechi *et al.*, 2000). Gandolfi *et al*. and Pradhan *et al*. both reported a significant percentage of thyroid cancer in MNG which was 13.7% and 13.6%, respectively (Gandolfi *et al.*, 2004; Pradhan *et al.*, 2011).

3.2.5 Thyroid malignancy in toxic versus non-toxic goiter.

A meta-analysis was performed comparing the incidence of thyroid cancer in patients who underwent surgery for toxic and nontoxic nodular goiter. Four studies were recruited in the meta-analysis with a total of 1,964 subjects undergoing thyroidectomy for benign thyroid diseases were analyzed. Among 1,964 subjects, 520 patients had toxic MNG or toxic adenoma and 1,444 had non-toxic MNG or STN. There was no significant differences in the risk of incidental thyroid cancer in patients with toxic MNG vs non-toxic MNG, toxic adenoma vs non-toxic STN, and toxic versus non-toxic nodular goiter (Negro *et al.*, 2013). Smith *et al*. reported as high as 18.3% of overall incidence of thyroid cancer in patients operated for toxic nodular goiter. This study also revealed a significantly higher cancer rate in toxic MNG than toxic STN (21% vs. 4.5 %, $P < 0.05$) (Smith *et al.*, 2013).

Study in endemic country revealed an almost similar finding which 10.1% of thyroid malignancy was found in patients with hyperthyroidism who underwent thyroid surgery. Occult papillary thyroid cancer was the most common type of malignancy found and accounted for 62.9% of all cancer diagnosed. The prevalence of carcinoma was 11.6% in toxic MNG, 7.7% in toxic STN, and 7.1% in patients with Graves' disease (Karagulle *et al.*, 2009).

3.3 Pre-operative diagnosis of thyroid malignancy

3.3.1 Ultrasonography

Wharry *et al*. performed a study to determine the accuracy of pre-operative US in diagnosing thyroid malignancy for patients with nodule ≥ 4cm. There was 20% risk of malignancy in patients who had no suspicious US features pre-operatively. The author concluded that the absence of suspicious US features did not reliably exclude malignancy and proposed for surgery in patients with thyroid nodule ≥ 4cm (Wharry *et al.*, 2013).

3.3.2 FNAC

A retrospective study to determine the risk of malignancy in non-diagnostic US-guided FNAC in MNG was performed and showed that 12.6 % of patients had malignancy from post-operative pathology results. Risk of malignancy in non-diagnostic FNAC despite US-guidance is still high and should be informed to the patient (Akgul *et al.*, 2011).

3.4 Surgical complications in thyroidectomy

A retrospective study in Greece regarding the surgical complications in 2,043 patients who underwent thyroid surgery between 1996 and 2007 indicated that transient RLN palsy occurred in 1.6% and permanent RLN palsy in 0.9% of patients. The rates of transient and permanent hypoparathyroidism were 27.8% and 4.8%, respectively. From this study, specimen weight was one of the independent predictor for transient hypocalcaemia but not permanent hypoparathyroidism following thyroidectomy with odd ratio of 1.6 (p=0.02). Other less common complications namely wound infection and hematoma occurred in 0.3% and 1.3% of patients, respectively (Karamanakos *et al.*, 2010).

Study by Gardiner et al. regarding surgical complications for thyroidectomy published in year 1995, 64 (14%) out of a total of 474 patients underwent thyroidectomies had large MNGs ≥ 100g. There was no perioperative mortality. Complications included permanent unilateral vocal cord paralysis in two patients (3.1%), permanent hypoparathyroidism in two (3.1%) and temporary emergency tracheostomy in one individual (1.6%) (Gardiner and Russell, 1995). Recent literature regarding complications of thyroidectomy for large goiter revealed a higher rate of difficult intubation, tracheostomy, and longer hospital stay especially if the surgery was performed for huge goiters and malignant disease. This study compared the complication rate in patients with goiters ≤ 400g and > 400g. The post-operative complications namely hemorrhage, tracheal injury, oesophageal injury, temporary hypocalcemia, temporary hoarseness, permanent hypoparathyroidism, and permanent RLN palsy did not differ significantly between the two groups (Agarwal *et al.*, 2012).

3.5 Indication for thyroid surgery

According to AACE/AME/ETA Guidelines 2010, the indication for surgery in thyroid nodule are presence of local pressure symptoms, previous external irradiation, progressive nodule growth, suspicious US features, cosmetic issues and malignant disease (Gharib *et al.*, 2010). It was mentioned in the latest American Thyroid Association statement on surgical management of goiter that the indications for thyroidectomy are present of symptoms related to compression, suspicion for malignancy, prevention of complication from progressive enlargement or mediastinal extension, and for cosmesis (Chen *et al.*, 2013).

There were only few literatures stated the issues regarding large goiter. The management of large goiter is suboptimum and none of the pre-operative investigation can accurately rule out malignancy. The associate risks for thyroid malignancy in large goiter are the important demographic and clinical features to suggest the likelihood of a patient with large goiter to harbor a malignancy and require a proper management. Furthermore, surgical complication for large goiter should be minimal and comparable to the surgical complication for small goiter.

CHAPTER 4: MATERIALS AND METHODS

4.1 Study design and source population

This was a cross-sectional study of patients who had undergone thyroidectomy in the Department of Breast and Endocrine Surgery, Hospital Raja Perempuan Zainab II (HRPZ II), Kelantan, Malaysia from January 2007 to May 2013. Recruitment of subjects was done based on the record of the list of patients who underwent thyroidectomy. The data of patients was retrieved from patients' medical records.

4.2 Eligible subjects

All patients who fulfilled the inclusion and exclusion criteria were recruited

Inclusion criteria:

- All patients who have undergone thyroidectomy (total and hemithyroidectomy) during the duration of study.

Exclusion criteria:

- Patient underwent isthmectomy, subtotal and near total thyroidectomy.
- Patient underwent completion thyroidectomy with prior history of surgery for thyroid cancer (only the first surgery was recruited).
- Patient underwent excision of recurrent nodule with prior history of surgery for thyroid (only the first surgery was recruited).
- Patient without thyroid enlargement who underwent total thyroidectomy for thyroid cancer which the diagnosis of thyroid cancer was made from the metastatic lesion.

Universal sampling method was applied to get the final study subjects. The patients with missing case notes or incomplete data were excluded from the study. Exclusion due to incomplete data only applied for important information such as weight of thyroid gland, variables involved in the analysis (age, sex, pressure symptoms, thyroid function status, nodularity), and histopathology result of resected specimen.

4.3 Sample size

Sample size estimation was calculated using single proportion formula for prevalence of large goiter (research question 1) and prevalence of malignancy in large goiter (research question 2). The calculation was to achieve a 95% confidence interval of absolute precision +/- 5% with 5% level of significant. 20% non-respondents was expected and added to achieve the final estimated sample size.

Estimated sample size for research questions number 3 and 4 which involved 2 means or 2 proportions was calculated using Power and Sample Size Calculation software version 3.0.10. The power of study was set at 80% ($1-\beta = 0.8$) with the significance level of 5% ($\alpha = 0.05$). Each associate factor for thyroid malignancy was calculated separately and 20% of non-respondents were included. The largest estimated sample size was taken as the target sample size needed for this study. Calculated sample size was 590 patients. The target sample size was achieved in this study and the total study subjects were 614. (See detail sample size calculation in Appendix A)

4.4 Research protocol

The study protocol was reviewed and approved by the Human Research and Ethics Committee, School of Medical Sciences, Universiti Sains Malaysia (Appendix B) as well as the Medical Review and Ethics Committee (MREC), Ministry of Health Malaysia (Appendix C). A list of patients who underwent thyroidectomy from January 2007 through May 2013 was obtained from the record in the operation theater. Patients who fulfilled the inclusion and exclusion criteria were recruited in the study. Their medical records were reviewed retrospectively.

In HRPZ II, patients who indicated and agreed for surgery were scheduled for elective surgery. Occasionally, emergency thyroidectomies were performed for patients with obstructive goiter that required ventilation. For elective cases, a routine history taking and physical examination were performed to obtain basic demographic data, to assess the presence of pressure symptom, to check the status of thyroid function and to examine the thyroid enlargement. Biochemical test for thyroid function was taken for each patient routinely, and presence of hyperthyroidism or hypothyroidism was treated to ensure euthyroidism at the time of surgery. Pre-operative ultrasonography and FNAC were performed only for those who indicated. FNAC were performed without ultrasound-guided in HRPZ II. Computed Tomography scan (CT scan) were performed for patients with huge goiters or suspected substernal goiters. Indirect laryngoscopy was performed pre-operatively for all patients to assess the vocal cords function.

The thyroid surgery was performed by either the endocrine surgeon or the trainee in endocrine surgery with supervision. The operation was performed by making a collar

incision two finger breadths above the sternal notch. Adrenaline was infiltrated before the skin incision. Superior and inferior subplatysmal flaps were raised from the thyroid cartilage to the sternal notch. The strap muscles were not routinely divided except for large goiter. The middle thyroid veins were ligated and divided if present. The superior thyroid vessels were individually ligated and divided. The RLN was identified and preserved. Inferior thyroid artery was ligated and divided. Identification of all parathyroid glands was preferred. Inadvertent parathyroid gland removal was followed by autotransplantation into the ipsilateral sternocleidomastoid muscle. Procedure was completed according to the extent of surgery.

Weighing of resected thyroid gland was performed immediately after the removal from the neck before it was placed in the hypertonic Formalin to avoid drying from osmotic effect. Suction drain was routinely inserted and removed when the 24 hours drainage was < 30ml. Patients were monitored closely after the surgeries for any post-operative complications. Routinely, serum calcium levels were checked at 6 hours post-operatively and the day after the operation. Hypocalcaemia was treated with oral calcium supplementation with or without Vitamin D analogues. Intravenous administration of calcium gluconate was given for patients with obvious clinical symptoms and signs of hypocalcaemia. Post-operative follow up for patients was at one month initially and three monthly interval afterwards. Thyroid function test, serum calcium level and indirect laryngoscopy examination were only performed when indicated.

In this study, patients were divided into groups with large or small goiter according to the weight of the resected thyroid glands. The diagnosis of thyroid malignancy was made based on the final histopathological report. The proportion of large goiter and the

proportion of thyroid malignancy in large goiter were recorded. The associate factors for thyroid malignancy in large goiter were analyzed. The variables included in the study were age and sex of patients, presence of pressure symptoms, thyroid function status, and nodularity of the thyroid gland. The follow up for surgical complications was performed on the sixth month after the surgery for this study.

4.5 Data collection

Permission from the Director of HRPZ II for retrieving the patients' medical records from record office was officially granted prior to the data collection activities. Data collected was recorded in a pre-formatted data collection form (Appendix D). The data recorded include patients' demographic data (Age, sex and ethnics), pre-operative information (pressure symptoms, nodularity of goiter, thyroid function status and FNAC result), operative information (date and duration of procedure, indication for surgery, type of surgical procedure, seniority of the surgeon, the weight of resected specimen and intra-operative surgical complication), post-operative surgical complication (temporary hypocalcaemia, permanent hypoparathyroidism, RLN palsy, haemorrhage, SSI, other organ injury and death), and final histopathological diagnosis after surgery.

4.6 Definition in the study

4.6.1 Definition of large goiter

Large goiter was defined by a resected specimen of more than or equal to 50g in hemithyroidectomy and more than or equal to 100g in total thyroidectomy. Total thyroidectomy was done by extracapsular dissection removing both of the thyroid lobes, isthmus and pyramidal lobe. Hemithyroidectomy was performed by removing unilateral thyroid lobe including the isthmus and pyramidal lobe.

4.6.2 Pressure symptoms

Pressure symptoms for goiter include discomfort, dysphagia, various degrees of difficulties in breathing and hoarseness of voice. Patients were categorized into 2 groups according to whether the pressure symptom was present or not without considering the type and duration of the symptoms.

4.6.3 Nodularity of thyroid gland

A goiter was classified into diffuse or nodular goiter. Nodular goiter was further classified into STN and MNG. MNG was defined as goiter with two or more nodules.

4.6.4 Thyroid function status

Patient with goiter may have different functional status. Definition of toxic goiter is determined by the laboratory thyroid function test (TFT) of elevated tri-iodothyronine (T3), elevated thyroxine (T4) and/ or suppressed thyroid stimulating hormone (TSH) or patient was on anti-thyroid medication before the surgery. Hypothyroidism was diagnosed by low

T3 and/ or T4 and/ or high TSH or patient was on thyroxine replacement. Euthyroid goiter included patient with normal TFT and without being treated with medication.

4.6.5 Temporary hypocalcaemia and permanent hypoparathyroidism

Temporary hypocalcaemia was considered when patient was symptomatic, corrected serum total calcium level was less than 2.0 mmol/l, requiring calcium and/or vitamin D supplements but with all symptoms resolved within 6 months post-operation. Permanent hypoparathyroidism was defined as hypocalcaemia that persists for more than 6 months and need regular calcium and vitamin D supplements.

4.6.6 RLN palsy

Temporary vocal cord dysfunction was not included in this study. Persistent hoarseness after six months post-operation was the indication to subject patient to indirect laryngoscopy examination by Ear, Nose and Throat (ENT) surgeon. Permanent RLN palsy was defined as presence of sustained immobility of the vocal cords six months after the surgery. Vocal cord palsy before the surgery was not counted as the surgical complication in this study.

4.6.7 Haemorrhage and SSI

Definition of haemorrhage ranged from acute bleeding intra-operatively, bleeding shortly after the surgery that needed emergency exploration to haematoma with or without surgical evacuation. Definition of SSI was according to the Centers for Disease Control & Prevention 1992 (Appendix E)(Horan *et al.*, 1992).

4.7 Data analysis

Data entry and analysis was done using Statistical Package for Social Science (SPSS) version 20.0. For descriptive analysis, categorical variables were expressed as frequencies (n) and proportions (%) while numerical variables were reported as mean with standard deviations (SD) or median with interquartile range (IqR). The prevalence of large goiter and prevalence of thyroid malignancy in large goiter were described as frequencies (n) and proportions (%)

The association between large goiter and thyroid malignancy was examined by comparing the proportions with Chi-square test. The demographic (age, sex) and clinical (nodularity, pressure symptom, thyroid function status) variables were analyzed as the associate factors for thyroid malignancy in large goiter. In univariable analysis, independent variables were initially assessed individually using the Simple Logistic Regression to determine the significant of each variable in predicting its association with thyroid malignancy. Odds Ratio (OR) and respective 95% Confidence Intervals (CI) were calculated for all clinical parameters. In multivariable analysis, Multiple Logistic Regression was applied. Preliminary main effect model was created with Forward Likelihood Ratio (LR) on all the clinical important and significant variables. Multicollinearity and interaction were checked to obtain the preliminary final model. The final model was checked for fitness using the Hosmer-Lemesshow test, classification table to count for overall correctly classified percentage, and the Receiver Operating Characteristic (ROC) curve to check for the area under ROC curve. The adjusted Odds Ratio was obtained from the final model. The level of statistical significance was set at $p < 0.05$.

4.8 Methodology Flow Chart